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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
DUFFY, BRADLEY	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/524,520	LOIBNER ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-10,12-15,17-22,25-27,29-32,34-43 and 46-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-10,12-15,17-22,25-27,29-32,34-43 and 46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 6, 2009, has been entered.

2. The amendment filed December 15, 2008, is acknowledged and has been entered. Claims 1, 29, 48 and 49 have been amended.

3. Claims 1-5, 7-10, 12-15, 17-22, 25-27, 29-32, 34-43 and 46-49 are pending in the application and are under examination. Notably, while claims 1-5, 7-10, 12-15, 17-22, 25-27, 29-32, 34-43 and 46-48 were previously withdraw from further consideration as being drawn to a non-elected invention, claims 1, 29, 48 have been amended to recite that the administration of the antibody is carried out during surgery which reads on the invention elected on May 24, 2007, which is drawn to methods for the intraoperative treatment of tumors comprising administering an antibody specific for Lewis Y during surgery. For this reason, these claims are again under examination, and Applicant is reminded that the restriction requirement has not been withdrawn.

Priority

4. With regards to the issue of priority, Applicant has supplied a verified translation of foreign application Austria A 1217/2002 on November 6, 2008, and this document is sufficient to establish priority of the instant claims to the filing date of this foreign application, which is August 12, 2002.

Grounds of Objection and Rejection Withdrawn

5. Unless specifically reiterated below, the grounds of objection and rejection set forth in the previous Office action mailed August 7, 2008, have been obviated or rendered moot by Applicant's amendment and/or arguments filed November 11, 2008 or December 15, 2008.

Grounds of Objection Maintained

Claim Objections

6. The objection to Claim 30 and 49 as being drawn in the alternative to the subject matter of non-elected inventions (i.e., methods of administering an antibody prior to surgery or methods of administering an antibody prior to surgery and during surgery), is maintained.

In this case, Applicant has submitted at page 9 of the response filed December 15, 2008, that the restriction requirement is being improperly applied as the subject matter of claim 49 has a special technical feature over the prior art.

In response, this argument is not found persuasive because as previously set forth in the restriction requirement mailed April 11, 2007, the subject matter of claim 1, i.e., administering an antibody direct against a tumor-associated antigen during surgery does not define a contribution over the prior art. Notably, this is also evidenced by the below prior art rejections of the claims.

Appropriate correction is required.

New or Reinstated Grounds of Objection

Claim Objections

7. (a) Claims 17 and 26 are objected to as being drawn in the alternative to the subject matter of a non-elected invention (i.e., the inventions of Group I-III and V-VII).

(b) Claims 30 and 31 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the

claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In this case, these claims recite administering the Lewis Y antibody during the surgical intervention, yet the preceding claim is already necessarily drawn to administering a Lewis Y antibody during surgery as the Lewis Y antibody is administered during surgery. Claim 30 is also objected to because a proper dependent claim shall not conceivably be infringed by anything which would not also infringe the basic claim. Notably, claim 29 requires that the antibody be administered during surgery, so the recitation in claim 30 that the antibody is administered immediately before the surgical intervention does not properly limit the administration step of claim 29. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

(c) Claim 17 is objected to for reciting "Lews Y". It appears that this is a typographical error and the claim should recite "Lewis Y".

Appropriate correction is required.

New or Reinstated Grounds of Rejection

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-5, 7-10, 12-15, 17-22, 25-27, 29-32, 34-43 and 46-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5, 7-10, 12-15, 17-22, 25-27, 29-32, 34-43 and 46-49 are indefinite in the recitation of "wherein immunocomplexing of tumor cells" in claims 1, 29, 48 and 49. This recitation renders the claims indefinite because the immunocomplexing referred to

in the wherein clause lacks antecedent basis in the process. Therefore, it cannot be determined which (if any) immunocomplexing step is being referred to in the wherein clause. Furthermore, because the wherein clause recites immunocomplexing, but the process steps do not refer to an immunocomplexing step, the claim is indefinite for omitting an essential step. Therefore, these claims fail to delineate the metes and bounds of the subject matter regarded as the invention with the clarity and particularity necessary to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

Accordingly, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. The rejection of claims 1-5, 7-8, 10, 12-15, 18-19, 22, 46, 48 and 49 under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,716,595 (of record), is maintained.

The claims are herein drawn to methods comprising administering a preparation of an antibody against a tumor associated antigen and at least one pharmaceutically acceptable carrier to patients during surgery. Notably, as set forth above because the immunocomplexing referred to in the wherein clause lacks antecedent basis in the process steps it cannot be determined which (if any) immunocomplexing step is being referred to and therefore, the claims are broadly, but reasonably being interpreted to only require that the preparation be administered to a patient during surgery. The

claims are further drawn to the antibody being directed against a protein surface antigen of an epithelial tumor cell (claims 3 and 4), administering an antibody mixture comprising antibodies having a specificity for tumor-associated antigens (Claim 5), the antibodies being derived from murine, chimeric, humanized or human sources (claim 8), the antibodies having a Kd value below 10^{-9} mol/l (claim 19), the antibodies being administered in a dose of at most 2 mg (claim 22) and the antibodies being administered locally (claim 10). Additionally, the claims are drawn to the surgery being carried out for biopsy and/or removal of the tumor or to determine the malignancy of the tumor (claims 12 and 13).

Claim 48 is herein drawn to methods comprising administering to a patient during surgery a preparation consisting of an antibody directed against a tumor-associated antigen, an adjuvant and at least one pharmaceutically acceptable carrier selected from the group consisting of an auxiliary substance, a buffer, a salt and a preservative whereby immunocomplexing of tumor cells within the scope of the surgical intervention inhibits dissemination of tumor cells, and wherein said immunocomplexing activates an antibody-dependent cellular cytotoxicity effector function and a complement dependent cytotoxicity effector function. Notably, while the term "adjuvant" is not expressly defined in the specification, the scope of the term is being interpreted in light of the disclosure at page 16, which states: "The combination with known adjuvant treatment methods is quite common." Accordingly, an adjuvant is broadly, but reasonably being interpreted to include any other substance which might be administered in combination with an antibody, such as another antibody have specificity for a tumor associated antigen, as set forth in claim 5.

Claim 49 is herein drawn to methods comprising administering to a patient during surgery a preparation consisting of an antibody directed against a tumor-associated antigen and at least one pharmaceutically acceptable carrier selected from the group consisting of an auxiliary substance, a buffer, a salt and a preservative whereby immunocomplexing of tumor cells within the scope of the surgical intervention inhibits dissemination of tumor cells, and wherein said immunocomplexing activates an

antibody-dependent cellular cytotoxicity effector function and a complement dependent cytotoxicity effector function.

At page 9 of the amendment filed December 15, 2008, Applicant has traversed this ground of rejection.

In this traversal, Applicant appears to be arguing at page 10, that US Patent No. 5,716,595 does not anticipate the claimed invention because the method of US Patent No. 5,716,595 is drawn to administering 0.01 to 20 mg of an antibody, while the present invention utilizes a high dose of at least 50 mg.

In response to applicant's argument that the reference fails to show certain features of applicant's invention, it is noted that the features upon which applicant relies (e.g., administering a dose of at least 50 mg) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant's arguments that the methods of US Patent No. 5,716,595 have different intended uses for "photodynamic detection" or "photodynamic therapy" are also not found persuasive, because as explained in the previous Office action, US Patent No. 5,716,595 teaches methods for the intraoperative treatment of tumors comprising administering tumor-associated antibodies to patients *during surgical treatments* (see entire document, e.g., column 10, lines 31-61 and column 13, lines 8-18). Notably, according to Dorlands Medical Dictionary, the term "intraoperative" is defined as "occurring during a surgical operation" (*Copyright 2007. An Elsevier publication. All rights reserved.*) (see Exhibit A attached to the office action mailed August 7, 2008) and therefore, it is apparent that US Patent No. 5,716,595 teaches administering tumor-associated antibodies ***during*** surgery. Furthermore, at column 3, lines 25 to 31, US Patent No. 5,716,595 sets forth the following: "a method for close-range tumor detection and treatment during an operative, intravascular or endoscopic procedure. The method comprises injecting a patient subject to such a procedure parenterally with an effective amount of a labeled protein which specifically binds a substance produced by or

associated with a targeted tumor"[1]. While this particular disclosure does not expressly identify labeled antibodies as such a labeled protein, other disclosures in US Patent No. 5,716,595 teach that labeled antibodies are species of labeled proteins (see e.g., column 9, lines 25-47). Finally, US Patent No. 5,716,595 teaches sterile injectable preparations for human use comprising labeled antibody which would inherently comprise at least one auxiliary substance, buffer, salt or a preservative. Furthermore, US Patent No. 5,716,595 teaches that the antibodies are directed against epithelial tumor associated surface antigens or tumor associated antigens, such as antibodies directed against tumor associated surface antigen CEA and/or the tumor associated antigen CSAp (e.g., column 13, lines 8-18). Additionally, US Patent No. 5,716,595 teaches murine, human, humanized or chimeric antibodies (e.g., column 6, lines 51-57 and column 13, lines 1-7) and administering at most 2 g of an antibody (column 15, lines 43-50). Finally, Goldenberg et al teach that surgeries are carried out to determine malignancy and/or to remove and/or treat the tumor (e.g., column 6, lines 25-35).

As evidenced by Cellular and Molecular Immunology, (of record) for antibodies specific for an antigen of interest, the binding constant (Kd) usually varies from about 10^{-7} M to 10^{-11} M (page 54). Accordingly, although US Patent No. 5,716,595 do not expressly teach using an antibody during surgery that binds, for example, the tumor associated surface antigen CEA and/or the tumor associated antigen CSAp, which has a binding constant below 10^{-8} mol/l, absent a showing of any difference, the antibodies used during surgery disclosed by the prior art are deemed the same as the claimed antibodies used during surgery.

Finally, Applicant has argued at pages 10 and 11, that the Examiner has characterized the scope of the claims incorrectly because the claims recite "antibody" as opposed to "antibody derivative", and the specification only discusses "antibodies of any type" as being "monospecific or polyspecific monoclonal antibodies" as page 13. In response, this argument is not found persuasive because the specification does not expressly limit the term "antibody" to "monospecific or polyspecific monoclonal

[1] Underlining added

antibodies" as this recitation is merely exemplary and not exculsice. Notably, this paragraph further sets forth that the term "antibody" refers to chemically, biochemically or molecular-biologically produced antibodies and one of skill in the art would recognize that labeled antibodies fall within the scope of the term "antibody" based on this non-limiting definition.

For these reasons, the processes of US Patent No. 5,716,595 remain manipulatively and materially indistinguishable from the claimed processes. Thus, absent a showing of any difference, the claimed processes are still deemed the same as that disclosed in the prior art.

Accordingly, while Applicant's arguments have been carefully and completely considered it is for these reasons and as further explained in the previous Office actions, that the rejection of claims 1-5, 7-8, 10, 12-15, 18-19, 22, 46, 48 and 49 under 35 U.S.C. 102(b), as being anticipated by US Patent No. 5,716,595, is maintained.

12. The rejection of claims 1-5, 7-8, 10, 12-15, 18-19, 48 and 49 under 35 U.S.C. 102(b) as being anticipated by US Patent No. 6,107,102 (of record), is maintained.

The instant claims are described in the above rejection of the claim as being anticipated by US Patent No. 5,716,595.

At page 11 of the amendment filed December 15, 2008, Applicant has traversed this ground of rejection.

In this traversal, Applicant appears to be arguing that the antibodies linked to a microdevice of US Patent No. 6,107,102 are essential to the invention of US Patent No. 6,107,102 and are not within the scope of the term "antibody" used in the instant claims.

In response, this argument is not found persuasive, because the specification does not expressly limit the term "antibody" to exclude antibodies linked to microdevices as the specification says the term "antibody" includes "antibodies of any type" and further sets forth that the term "antibody" refers to chemically, biochemically or molecular-biologically produced antibodies (see page 13), Notably, based on this non-limiting definition one of skill in the art would recognize that antibodies linked to a microdevice fall within the scope of the term "antibody" because they would be

considered a type of antibody that has been chemically, biochemically or molecular-biologically produced.

Accordingly, it is maintained that US Patent No. 6,107,102 teaches methods for the intraoperative treatment of epithelial derived tumors comprising locally administering "antibodies" in combination with pharmaceutically acceptable carriers and/or other adjuvant substances to patients during tumor removal surgery (see entire document, e.g., column 10, lines 31-61, column 14 and column 19), wherein the antibodies are directed against epithelial tumor associated surface antigens or tumor associated antigens, such as antibodies directed against the tumor associated surface antigen TAG-72 and/or the tumor associated antigen collagen IV (see entire document, e.g., column 19, line 57 to column 20, line 15) and column 11, lines 34-46). Additionally, US Patent No. 6,107,102 teach murine or human antibodies (e.g., column 11, lines 34-46 and column 16, lines 9-13).

Therefore, the processes of US Patent No. 6,107,102 remain manipulatively and materially indistinguishable from the claimed processes. Thus, absent a showing of any difference, the claimed processes are still deemed the same as that disclosed in the prior art.

Accordingly, while Applicant's arguments have been carefully and completely considered it is for these reasons and as further explained in the previous Office actions, that the rejection of claims 11-5, 7-8, 10, 12-15, 18-19, 48 and 49 under 35 U.S.C. 102(b), as being anticipated by US Patent No. 6,107,102 is maintained.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29

USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. The provisional rejection of claims 1-5, 7-8, 11-15, 17-19, 22, 25-27, 29-32, 34-35, 38-43, 48 and 49 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 9-10, 14, 16-21 and 24-27 of copending Application No. 10/558,166, is maintained.

At page 12 of the amendment filed December 15, 2008, Applicant submits that this rejection will be addressed upon the finding of patentable subject matter in the present application.

In response, the pending claims in these applications have not been amended sufficiently to overcome this provisional rejection. Notably, the claims of copending Application No. 10/558,166 are drawn to methods administering Lewis antibodies to patients during surgery (see claims 14 and 21 in particular) and this provisional rejection will be maintained until it is appropriately resolved.

Grounds of Rejection Reinstated

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived

by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1, 9, 17, 20, 25-27, 29-32, 35-40, 43 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,716,595 (Goldenberg et al, published 1998) (of record), in view of Schlimok et al (Eur. J. Can., 31A(11):1799-1803, 1995) (of record)and Crisan et al (Molecular Diagnosis, 5(1):33-38, 2000) (of record).

The claims are herein drawn to methods of administering preparations of a Lewis Y antibody and at least one pharmaceutically acceptable carrier to patients during surgery. The claims are further drawn to the antibody being administered systematically in a dose of at least 100 mg, administered in a single dose of at most 2 mg or administered locally, the antibodies being derived from murine, chimeric, humanized or human sources. Additionally, the claims are drawn to the surgery being

carried out for biopsy and/or removal of the tumor or to determine the malignancy of the tumor.

US Patent No. 5,716,595 teaches that methods for administering antibody compositions during surgery are known in the art and that what is set forth in the above 102 (b) rejection.

However, US Patent No. 5,716,595 does not expressly teach administering preparations of Lewis Y antibodies to patients or administering at least 100 mg of an antibody to a patient.

These deficiencies are made up for in the teachings of Schlimok et al and Crisan et al. Schlimok et al teach that disseminated breast epithelial tumor cells express a surface antigen named Lewis Y by detecting immunocomplexes of Lewis Y and a Lewis Y antibody and that administering preparations of Lewis Y antibodies in buffers to breast cancer patients systemically in doses of 100 mg inhibits tumor cell dissemination in patients with large numbers of disseminated tumor cells present in their bone marrow (see entire document, e.g., abstract, page 1802, Tables 3 and 4). Crisan et al teach that breast tumor epithelial cells can be mobilized to disseminate from the tumor site **during** breast surgery as patients monitored for disseminated tumor cells before and after breast surgery show increased levels of circulating disseminated cells after surgery (see entire document, e.g. abstract and page 36, left column).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to systematically administer preparations of monoclonal, human, humanized or chimeric Lewis Y antibodies in buffers to patients during surgery in doses of 100 mg or more during surgery, as Schlimok et al teach that a Lewis Y antibody that **inhibits** breast cancer dissemination and Crisan et al teach that **surgery** can cause breast epithelial cell dissemination.

One of ordinary skill in the art would have been motivated at the time the invention was made to do so, and would have had a reasonable expectation of success, because Crisan et al teach that surgery increases the number of disseminated cells and Schlimok et al teach that Lewis Y antibodies can be systemically administered to breast

cancer patients and that these antibodies **inhibit** tumor cell dissemination in patients with increased numbers of circulating cells.

Additionally, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to locally administer the preparations of Lewis Y antibody to the tumor site as US Patent No. 5,716,595 teaches methods of treating tumors by locally applying antibodies directed to tumor antigens and Crisan et al teach that tumor cells are mobilized to disseminate during surgery.

One of ordinary skill in the art would have been motivated at the time the invention was made to do so, and would have had a reasonable expectation of success, because Crisan et al teach that tumor cells are mobilized during surgery and therefore one of skill in the art would have been motivated to administer the preparations of Lewis Y antibody locally according to the methods of US Patent No. 5,716,595 to prevent this mobilization.

Notably, this rejection has been reinstated because Applicant has amended the above claims which had been withdrawn from consideration as drawn to a non-elected invention, so that they are now once again drawn to the elected invention. Furthermore, while Applicant's arguments presented at page 11 in the response filed January 14, 2008, that the primary reference is deficient because it fails to teach administering antibodies during surgery have been fully and carefully considered, these arguments were not found not persuasive.

Notably, in response to applicant's arguments against US Patent No. 5,716,595 individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, because Crisan teaches that surgery increases the number of disseminated tumor cells, while Schlimok teaches Lewis Y antibodies that inhibit dissemination of tumor cells, one of skill in the art would not have found it inventive to administer such antibodies during surgery to inhibit dissemination because one of skill in the art would have immediately recognized that there was a predictable solution to solve the art known problem of surgery **increasing** tumor cell dissemination,

i.e., administering during surgery Lewis Y antibodies because such antibodies are known in the art to inhibit tumor cell dissemination.

For these reasons, after considering the prior art as a whole and carefully and fully considering Applicant's response, the invention as a whole was obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and this rejection has been reinstated.

18. Claims 21, 34, 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,716,595 (Goldenberg et al, published 1998) (of record), in view of Schlimok et al (Eur. J. Can., 31A(11):1799-1803, 1995) (of record) and Crisan et al (Molecular Diagnosis, 5(1):33-38, 2000) (of record) as applied to claims 1, 9, 17, 20, 25-33 and 35-36 and 38-40 above, and further in view of US Patent 5,792,456 (Yelton et al, published 1998) (of record).

The claims are further drawn to the Lewis Y antibodies having a Kd value below 10^{-8} mol/l or the Lewis Y antibody being administered at a dose of at least 200 mg.

US Patent No. 5,716,595, Schlimok et al and Crisan et al teach that which is set forth above.

However, neither US Patent No. 5,716,595, Schlimok et al and Crisan et al explicitly teach administering to patients Lewis Y antibodies having a Kd value below 10^{-8} mol/l or the Lewis Y antibody being administered at a dose of at least 200 mg.

Yelton et al teach methods of administering preparations of Lewis Y antibodies to patients and Lewis Y antibodies with a Kd value below 10^{-8} mol/l (see entire document, column 33, line 61 to column 36, line45) and the Lewis Y antibody being administered at a dose of at least 200 mg (e.g column 20, line 39 to column 22, line 47).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to furthermore treat patients during surgery with Lewis Y antibodies with Kd values below 10^{-8} mol/l and to administer the Lewis Y antibody at a dose of at least 200 mg.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to do so because

Lewis Y antibodies with a Kd values below 10^{-8} mol/l would have higher affinity for the disseminated tumor cells and higher doses of antibody would target more disseminated tumor cells. Thus, as Schlimok et al teach that Lewis Y antibodies inhibit tumor cell dissemination, one of skill in the art would have been motivated to use the higher affinity antibodies and dosing schedules of Yelton et al and as these higher affinity antibodies and dosing schedules were known in the art and one of skill in the art would have had a reasonable expectation of success in practicing the claimed methods.

Notably, this rejection has been reinstated because Applicant has amended the above claims which had been withdrawn from consideration as drawn to a non-elected invention, so that they are now once again drawn to the elected invention. Furthermore, while Applicant's arguments presented at page 11 in the response filed January 14, 2008, have been fully and carefully considered, these arguments were not found not persuasive for the reasons set forth above.

For these reasons, after considering the prior art as a whole and carefully and fully considering Applicant's response, the invention as a whole was obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and this rejection has been reinstated.

19. Claims 1, 9, 17, 20, 25-27, 29-32, 35-40, 43 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over by US Patent 6,107,102 (Ferrari et al, published 2000) (of record), in view of Schlimok et al (Eur. J. Can., 31A(11):1799-1803, 1995) (of record) and Crisan et al (Molecular Diagnosis, 5(1):33-38, 2000) (of record).

The claims are herein drawn to methods of administering preparations of a Lewis Y antibody and at least one pharmaceutically acceptable carrier to patients during surgery. The claims are further drawn to the antibody being administered systematically in a dose of at least 100 mg, administered in a single dose of at most 2 mg or administered locally, the antibodies being derived from murine, chimeric, humanized or human sources. Additionally, the claims are drawn to the surgery being carried out for biopsy and/or removal of the tumor or to determine the malignancy of the tumor.

US Patent 6,107,102 teaches that methods for administering antibody compositions during surgery are known in the art and that what is set forth in the above 102 (b) rejection. However, US Patent 6,107,102 does not expressly teach administering Lewis Y antibodies to patients or administering at least 100 mg of an antibody to a patient.

These deficiencies are made up for in the teachings of Schlimok et al and Crisan et al. These deficiencies are made up for in the teachings of Schlimok et al and Crisan et al. Schlimok et al teach that disseminated breast epithelial tumor cells express a surface antigen named Lewis Y by detecting immunocomplexes of Lewis Y and a Lewis Y antibody and that administering preparations of Lewis Y antibodies in buffers to breast cancer patients systemically in doses of 100 mg inhibits tumor cell dissemination in patients with large numbers of disseminated tumor cells present in their bone marrow (see entire document, e.g., abstract, page 1802, Tables 3 and 4). Finally, Schlimok et al teach chimeric Lewis Y antibodies (see e.g., abstract, page 1803). Crisan et al teach that breast tumor epithelial cells can be mobilized to disseminate from the tumor site **during** breast surgery as patients monitored for disseminated tumor cells before and after breast surgery show increased levels of circulating disseminated cells after surgery (see entire document, e.g. abstract and page 36, left column).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to systematically administer preparations of monoclonal, human, humanized or chimeric Lewis Y antibodies to patients during surgery in doses of 100 mg or more during surgery, as Schlimok et al teach that a Lewis Y antibody that **inhibits** breast cancer dissemination and Crisan et al teach that **surgery** can cause breast epithelial cell dissemination.

One of ordinary skill in the art would have been motivated at the time the invention was made to do so, and would have had a reasonable expectation of success, because Crisan et al teach that surgery increases the number of disseminated cells and Schlimok et al teach that Lewis Y antibodies can be systemically administered to breast cancer patients and that these antibodies **inhibit** tumor cell dissemination in patients

with increased numbers of circulating cells.

Additionally, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to locally administer preparations of Lewis Y antibody to the tumor site as US Patent 6,107,102 teaches methods of treating tumors by locally applying antibodies directed to tumor antigens and Crisan et al teach that tumor cells are mobilized to disseminate during surgery.

One of ordinary skill in the art would have been motivated at the time the invention was made to do so, and would have had a reasonable expectation of success, because Crisan et al teach that tumor cells are mobilized during surgery and therefore one of skill in the art would have been motivated to administer the Lewis Y antibody locally according to the methods of US Patent 6,107,102 to prevent this mobilization.

Notably, this rejection has been reinstated because Applicant has amended the above claims which had been withdrawn from consideration as drawn to a non-elected invention, so that they are now once again drawn to the elected invention. Furthermore, while Applicant's arguments presented at page 11 in the response filed January 14, 2008, that the primary reference is deficient because it fails to teach administering antibodies during surgery have been fully and carefully considered, these arguments were not found not persuasive.

Notably, in response to applicant's arguments against US Patent 6,107,102 individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, because Crisan teaches that surgery increases the number of disseminated tumor cells, while Schlimok teaches Lewis Y antibodies that inhibit dissemination of tumor cells, one of skill in the art would not have found it inventive to administer such antibodies during surgery to inhibit dissemination because one of skill in the art would have immediately recognized that there was a predictable solution to solve the art known problem of surgery **increasing** tumor cell dissemination, i.e., administering during surgery Lewis Y antibodies because such antibodies are known in the art to inhibit tumor cell dissemination.

For these reasons, after considering the prior art as a whole and carefully and fully considering Applicant's response, the invention as a whole was obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and this rejection has been reinstated.

20. Claims 21, 34, 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,107,102 (Ferrari et al, published 2000) (of record), in view of Schlimok et al (Eur. J. Can., 31A(11):1799-1803, 1995) (of record) and Crisan et al (Molecular Diagnosis, 5(1):33-38, 2000) (of record) as applied to claims 1, 9, 13, 17, 20, 25-33 and 35-40 above, and further in view of US Patent No. 5,792,456 (Yelton et al, published 1998) (of record).

The claims are further drawn to the Lewis Y antibodies having a Kd value below 10^{-8} mol/l or the Lewis Y antibody being administered at a dose of at least 200 mg.

US Patent No. 6,107,102, Schlimok et al and Crisan et al teach that which is set forth above.

However, neither US Patent No. 6,107,102, Schlimok et al and Crisan et al explicitly teach administering to patients Lewis Y antibodies having a Kd value below 10^{-8} mol/l or the Lewis Y antibody being administered at a dose of at least 200 mg.

Yelton et al teach methods of administering preparations of Lewis Y antibodies to patients and Lewis Y antibodies with a Kd value below 10^{-8} mol/l (see entire document, column 33, line 61 to column 36, line 45) and the Lewis Y antibody being administered at a dose of at least 200 mg (e.g column 20, line 39 to column 22, line 47).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to furthermore treat patients during surgery with Lewis Y antibodies with Kd values below 10^{-8} mol/l and to administer the Lewis Y antibody at a dose of at least 200 mg.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to do so because Lewis Y antibodies with a Kd values below 10^{-8} mol/l would have higher affinity for the disseminated tumor cells and higher doses of antibody would target more disseminated

tumor cells. Thus, as Schlimok et al teach that Lewis Y antibodies inhibit tumor cell dissemination, one of skill in the art would have been motivated to use the higher affinity antibodies and dosing schedules of Yelton et al and as these higher affinity antibodies and dosing schedules were known in the art and one of skill in the art would have had a reasonable expectation of success in practicing the claimed methods.

Notably, this rejection has been reinstated because Applicant has amended the above claims which had been withdrawn from consideration as drawn to a non-elected invention, so that they are now once again drawn to the elected invention. Furthermore, while Applicant's arguments presented at page 11 in the response filed January 14, 2008, have been fully and carefully considered, these arguments were not found not persuasive for the reasons set forth above.

For these reasons, after considering the prior art as a whole and carefully and fully considering Applicant's response, the invention as a whole was obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and this rejection has been reinstated.

Conclusion

21. No claims are allowed.

22. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Patent 5,624,659 (of record) teaches locally administering an antibody directed against the tumor-associated antigen, tenascin, into surgical resection cavities of glioblastoma patients during surgery. Weitz et al (Clin. Can. Res., 4:343-348, 1998) teach that colorectal cancer cells are present in systemic circulation at an increased rate during surgery and suggest administering high levels of antibodies against antigens on the tumor cells during surgery to inhibit dissemination of such cancer cells. Co et al (Can Res., 56:118-1125, 1996) teach a Lewis Y antibody that mediates ADCC and CDC when bound to human cancer cells.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
April 9, 2009